

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 1129WOORD01	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA416)	
International application No. PCT/EP 03/08676	International filing date (day/month/year) 06.08.2003	Priority date (day/month/year) 10.08.2002
International Patent Classification (IPC) or both national classification and IPC C07D401/04		
<p>Applicant ALTANA PHARMA AG</p>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
 - This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.
3. This report contains indications relating to the following items:
 - I Basis of the opinion
 - II Priority
 - III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV Lack of unity of invention
 - V Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI Certain documents cited
 - VII Certain defects in the international application
 - VIII Certain observations on the International application

Date of submission of the demand 17.02.2004	Date of completion of this report 16.04.2004
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kyriakakou, G Telephone No. +49 89 2399-7835

INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

International application No. PCT/EP 03/08676

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-29 as originally filed

Claims, Numbers

1-17 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- the description, pages:
- the claims, Nos.:
- the drawings, sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/EP 03/08676

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
 - the entire international application,
 - claims Nos. 16 and 17 in respect of industrial applicability

because:

 - the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - no international search report has been established for the said claims Nos.
2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - the written form has not been furnished or does not comply with the Standard.
 - the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-17
	No: Claims	
Inventive step (IS)	Yes: Claims	1-17
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-15
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP03/08676

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 16 and 17 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Cited Documents

1.1. Certain published documents (Rule 70.10)

WO-A-02085906 (=D1)
WO-A-02064584 (=D2)

1.2 Reference is made to the following Documents.

WO-A-0130777 (=D3)
WO-A-9931090 (=D4)
WO-A-9931071 (=D5)
WO-A-9831674 (=D6)
WO-A-9307146 (=D7)
J.Med. Chem. 2001,44,2523 (=D8)
J.Med. Chem. 2002,45,2520 (=D9)
J.Med. Chem. 2002,45,2526 (=D10)

The indicated designation is used throughout the examination procedure

3. Novelty

The present application and the prior art Documents D3-D10 relate to **2-N-substituted-pyridazinones**. The main structural difference resides in the nature of the "-N- substituent.

The subject matter of the present claims 1-17 can therefore be considered to be novel.

4. Inventive step

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP03/08676

4.1 The object of the present invention is to provide compounds useful as PDE4 inhibitorss.

4.2 In the light of the pharmacological tests comprised in the Description (28-29) it is considered as credible that a limited number of the claimed compounds have the alleged activity.

4.3 The prior art documents D3-D10 which disclose structurally similar pyridazinone derivatives having PDE4 inhibitory activity are considered to be especially relevant. With respect to the said prior art documents the main structural difference lies in the modification of the 2N--substituent of the pyridazinone. Taking the above into account it is evident for the person skilled in the art that the pyridazinone group is fundamental for the PDE4 inhibitory activity and further modification of the substituents results to more or less potent agents while the PDE4 inhibitory activity is maintained. The claimed compounds are therefore considered to be *prima facie* obvious and an inventive step cannot be acknowledged,

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D401/04 C07D405/14 A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 02 085906 A (ALTANA PHARMA AG) 31 October 2002 (2002-10-31) cited in the application page 31 -page 41; claims 1-13 ----	1-17
P, A	WO 02 064584 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 22 August 2002 (2002-08-22) cited in the application page 25 -page 36; claims 1-13 ----	1-17
Y	WO 99 31090 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 34 -page 38; claims 1-10 ----	1-17 -/-



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 2003	12/12/2003
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Kyriakakou, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 01 30777 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 3 May 2001 (2001-05-03) cited in the application page 21 -page 25; claims 1-10 ---	1-17
Y	WO 99 31071 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 24 June 1999 (1999-06-24) cited in the application page 32 -page 36; claims 1-10 ---	1-17
Y	WO 98 31674 A (BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH) 23 July 1998 (1998-07-23) cited in the application page 49 -page 55; claims 1-10 ---	1-17
Y	WO 93 07146 A (SYNTEX INC.) 15 April 1993 (1993-04-15) cited in the application page 162 -page 169; claims 1-33 ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective Phosphodiesterase (PDE4) inhibitors. 4. Resolution, Absolute Configuration and PDE4 Inhibitory Activity of cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2526-2533, XP002262562 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document ---	1-17
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors.3. In Vivo Antiinflammatory Activity of a New Series of N-Substituted cis-Tetra- and cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 45, no. 12, 6 June 2002 (2002-06-06), pages 2520-2525, XP002262563 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document ---	1-17
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARGARETHA VAN DER MEY ET AL.: "Novel Selective PDE4 Inhibitors. 2. Synthesis and Structure-Activity Relationships of 4-Aryl-Substituted cis-Tetra- and Cis-Hexahydrophthalazinones" JOURNAL OF MEDICINAL CHEMISTRY., vol. 44, no. 16, 2 August 2001 (2001-08-02), pages 2523-2535, XP002222951 AMERICAN CHEMICAL SOCIETY., US ISSN: 0022-2623 cited in the application the whole document -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08676

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 16 and 17 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat... Application No

PCT/EP 03/08676

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 02085906	A	31-10-2002	WO	02085906 A2		31-10-2002
WO 02064584	A	22-08-2002	CA	2438520 A1		22-08-2002
			EE	200300311 A		15-10-2003
			WO	02064584 A1		22-08-2002
			EP	1362044 A1		19-11-2003
WO 9931090	A	24-06-1999	AU	753576 B2		24-10-2002
			AU	2270199 A		05-07-1999
			CA	2314111 A1		24-06-1999
			EE	2000000335 A		15-10-2001
			WO	9931090 A1		24-06-1999
			EP	1042319 A1		11-10-2000
			HU	0004561 A2		28-03-2002
			JP	2002508368 T		19-03-2002
			PL	341239 A1		26-03-2001
			US	6380196 B1		30-04-2002
WO 0130777	A	03-05-2001	AU	1515101 A		08-05-2001
			BR	0014990 A		18-06-2002
			CA	2388119 A1		03-05-2001
			CN	1382137 T		27-11-2002
			CZ	20021457 A3		17-07-2002
			WO	0130777 A1		03-05-2001
			EP	1244654 A1		02-10-2002
			HU	0203487 A2		28-02-2003
			JP	2003512466 T		02-04-2003
			NO	20021959 A		29-05-2002
			SK	7232002 A3		10-09-2002
			TR	200201128 T2		21-08-2002
			US	6544993 B1		08-04-2003
			US	2003166655 A1		04-09-2003
			ZA	200203157 A		10-04-2003
WO 9931071	A	24-06-1999	AU	1760399 A		05-07-1999
			WO	9931071 A1		24-06-1999
WO 9831674	A	23-07-1998	AT	233247 T		15-03-2003
			AU	735934 B2		19-07-2001
			AU	5862998 A		07-08-1998
			BR	9806752 A		14-03-2000
			CN	1127487 B		12-11-2003
			DE	69811645 D1		03-04-2003
			DK	971901 T3		10-06-2003
			EA	2764 B1		29-08-2002
			EE	9900274 A		15-02-2000
			WO	9831674 A1		23-07-1998
			EP	0971901 A1		19-01-2000
			HU	0001541 A2		28-05-2001
			IL	130659 A		25-07-2002
			JP	2001508078 T		19-06-2001
			NO	993301 A		10-09-1999
			NZ	336573 A		27-10-2000
			PL	334561 A1		13-03-2000
			PT	971901 T		31-07-2003
			SI	971901 T1		31-10-2003
			SK	95199 A3		10-12-1999
			TR	9901653 T2		21-10-1999

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/08676

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9831674	A	US	6103718 A	15-08-2000
WO 9307146	A	15-04-1993	AT 183745 T AU 670544 B2 AU 2781592 A CA 2117059 A1 DE 69229874 D1 DE 69229874 T2 DK 612321 T3 EP 0612321 A1 ES 2105920 A1 ES 2135416 T3 FI 941567 A GR 3030969 T3 HU 66969 A2 HU 9500113 A3 IL 103388 A JP 3245165 B2 JP 7500321 T KR 263494 B1 MX 9205794 A1 NO 941210 A NZ 244660 A PT 100938 A , B WO 9307146 A1 US 5716954 A ZA 9207755 A	15-09-1999 25-07-1996 03-05-1993 15-04-1993 30-09-1999 09-12-1999 13-12-1999 31-08-1994 16-10-1997 01-11-1999 06-04-1994 30-11-1999 30-01-1995 28-06-1995 30-09-1997 07-01-2002 12-01-1995 01-08-2000 01-04-1993 05-04-1994 26-05-1995 29-10-1993 15-04-1993 10-02-1998 08-04-1994